

METHACYCLINE (RONDONMYCIN) IN GONORRHOEA*

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After more than 20 years penicillin remains the drug of first choice in the treatment of gonorrhoea. It offers a high cure rate. Curative dosages can be given in one injection in uncomplicated cases. It is relatively safe and it is cheap. On the other hand an increasing number of persons are found to be sensitive to penicillin and, with the increasing incidence of early syphilis, there is again the risk of masking concomitant or incubating forms of that infection. Furthermore, over the years a spiral of events can be discerned in alternating increasing failure rates and larger standard dosages. Thus, whereas 300,000 units of a moderately long-acting form of penicillin sufficed 20 years ago, schedules of 1·2 or 1·8 mega units are now commonplace and multiple dosage is employed by some.

The fear that the days of penicillin may be numbered in gonorrhoea therapy has led to trials of a wide range of antibiotics. Such drug trials are essential, not only to establish the best second choice but to show which of the many therapies available may perhaps be tomorrow's first choice.

Modifications of the basic tetracycline molecule has led to a variety of tetracyclines. This study is concerned with one of these, 6-methylene oxytetracycline, known also as methacycline. It is active against a wide range of Gram-positive and Gram-negative organisms, and is said to be more active against some organisms than tetracycline both *in vitro* and *in vivo* (Te-wen Chang and Weinstein, 1962). *In vivo* studies by Kunin (1962) suggest that at least, in part, this effect may be due to delayed renal excretion.

Patients Studied

A series of fifty males with acute uncomplicated urethral gonorrhoea attending during 1965 has been studied. The only element of selection was that there was

a chance of patients attending for reasonable follow-up. In practical terms this meant that selected patients were usually local residents. The average age was 27·7 years (range 16–51). 25 men were married, including twelve immigrants whose wives were still abroad. In eleven there was a history of 23 attacks of gonorrhoea; five had had nine attacks of non-gonococcal urethritis (NGU), three had previously been treated for syphilis, and one other for yaws. The source of infection in five was marital. In eight the posterior urethra was involved as determined by the two-glass urine test.

Management

The diagnosis of gonorrhoea was established by Gram-stained smears and specimens submitted for culture. Culture specimens were submitted in Stuart's transport medium for plating out on McLeod's heated blood agar. Sensitivity tests to a range of drugs were carried out by the disk method. The M.I.C. of penicillin and of methacycline was estimated by the tube method on 42 and 12 cultures respectively. The procedure was similar to that followed by the local laboratory when it took part in the M.R.C. study reported in 1961. Persistence or re-appearance of urethral discharge was investigated by the same routine.

As a routine a Wassermann reaction, Kahn test, and Reiter protein complement-fixation test were carried out in all cases; all were negative.

The group of fifty patients was studied in two comparable groups of 25, using two dosage schedules each totalling 900 mg. methacycline:

Regimen A—300 mg. by mouth every 8 hrs for 1 day, *i.e.* three doses.

Regimen B—150 mg. by mouth every 8 hrs for 2 days, *i.e.* six doses.

Successful treatment was defined as the absence of gonococci on follow-up examinations. A follow-up period of 3 months was the aim. Each patient was asked to attend twice in the week following the start of treatment and again at the end of a further week. Thereafter patients were invited to attend at extending intervals and a final blood test for syphilis was carried out after 3 months' observation.

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Results

Regimen A

There was response to therapy in 21 cases. Three men failed to respond and two of these also failed to respond to a routine penicillin dosage of 1.2 mega units aqueous procaine penicillin. The remaining member of the original group of 25 defaulted immediately after diagnosis and treatment. Of the 24 men who attended for follow-up (Table I), 21 (87.5 per cent.) were successfully treated as defined under "Management". Three men were found to be re-infected with gonorrhoea at 12 days, 4 weeks, and 8 weeks after treatment. Three men developed post-gonococcal NGU. The follow-up periods are shown in Table II.

TABLE I
RESPONSE TO METHACYCLINE THERAPY
IN MALE GONORRHOEA

Result	Cases Treated		Regimen	
	No.	Per cent.	A	B
Successful	43	87.7	21	22
Failure	6	12.3	3	3
Immediate Default ..	1	—	1	—

TABLE II
FOLLOW-UP OF MALES WITH GONORRHOEA TREATED
WITH METHACYCLINE

Follow-up	Total Cases	Regimen	
		A	B
3 days or more	49	24	25
1 week or more	44	20	24
2 weeks or more	37	17	20
4 weeks or more	23	12	11
9 weeks or more	10	4	6

The range of sensitivity to penicillin (23 cases) and methacycline (5 cases) is shown in Table III. Strains with a penicillin M.I.C. of 0.125 units/ml. or more are generally accepted as relatively insensitive. There were three such strains in this range. None of these strains occurred in men who failed to respond to treatment with methacycline.

There was no correlation between penicillin and methacycline sensitivity levels. The number available in each group, however, is small. Only one of the three cases of failure had a methacycline sensitivity determination (Table III).

Regimen B

There was response in 22 cases. Three men failed to respond but these were cured by current routine dosages of penicillin, *i.e.* 1.2 mega units of an aqueous procaine preparation.

Of the 25 men who attended for follow-up

TABLE III
SENSITIVITY LEVELS OF STRAINS OF GONOCOCCI UNDER
STUDY

Drug	Dosage	Strains	Regimen	
			A	B
Penicillin (units/ml.)	0.015	11	4	7
	0.03	14	8	6
	0.06	12	7	5
	0.125	3	2	1
	0.25	2	2	—
Methacycline (µg./ml.)	0.25	1	—	1
	0.5	3	2	1
	1	3	1	2
	2	1	1	—
	4	2	1	1
	8	2	—	2

(Table I), 22 (88 per cent.) were successfully treated as defined under "Management". Three men were found to be re-infected with gonorrhoea at 7, 14, and 26 days after treatment. Three men developed post-gonococcal NGU, one after re-infection with gonorrhoea. The follow-up periods are shown in Table II.

The range of sensitivity to penicillin (19 cases) and methacycline (7 cases) is shown in Table III. One strain only was found to be in the penicillin M.I.C. range of 0.125 units/ml. or more. It did not appear among the failure cases. None of the cases of failure were among those strains whose methacycline sensitivity level was determined.

Discussion

The response to a total dosage of 900 mg. methacycline was 87.7 per cent. This is not so good as the 100 per cent. response reported by Marmell, Sills, and Prigot (1962) using a similar total dosage in similar schedules in 25 patients. In the same trial these authors also reported that a schedule of 150 mg. every 6 hrs for 1 day resulted in eight failures in 46 patients.

No attempt was made in the present series to study response to methacycline by the double-blind method. We thought it of interest, however, to take as our yardstick of success the response rate to routine penicillin dosages employed in 1964 and 1965. A sample of fifty consecutive patients infected with gonococci of known penicillin sensitivity is shown in Table IV (opposite). In 1964, when the gonococcal population contained 18 per cent. of less sensitive strains, the response rate to 600,000 units aqueous procaine penicillin was 90 per cent. In 1965, when the gonococcal population contained 20 per cent. of less sensitive strains, the response rate to 1.2 mega units of aqueous procaine penicillin was 100 per cent. (Over the whole year's working however the cure rate was 95 per cent.).

TABLE IV

DISTRIBUTION OF PENICILLIN MIC IN GONOCOCCAL STRAINS IN SHEFFIELD TRIAL SERIES COMPARED WITH 1964 AND 1965 SAMPLES

Penicillin (units/ml.)			Series		
			Consecutive (1964)	Consecutive (1965)	Present Study (1965)
Sensitive	·008		2	1	—
	·015		9	7	11
	·03		12	14	14
	·06		18	18	12
	·125		8	8	3
	·25		—	2	2
	·5		1	—	—
Total			50	50	42
Relatively Insensitive	·125 and over	No.	9	10	5
		Per cent.	18	20	12

Judged by current clinical results, therefore, methacycline therapy in the dosages reported appears as a modest second best.

The trial series included only 12 per cent. less sensitive gonococci as judged by penicillin sensitivity levels. If such levels can be taken as a standard, the results found in the present series must be the most favourable which can be expected.

It is appreciated that lack of national or international standardization of sensitivity testing makes attempts at a dogmatic statement or firm recommendations unwise. We suggest, however, that it would be useful in future drug trials of penicillin or other antibiotics for workers to state at least the sensitivity to penicillin and other antibiotics of the strains under study, as well as the methods employed for such testing.

Summary

The need to test recently discovered antibiotics in gonorrhoea is indicated by the waning efficacy, even if marginal, of penicillin. A trial of methacycline in two dosage schedules is reported.

The response rates under two regimens, which were almost identical, averaged 87·7 per cent.

The suggestion is made that, in spite of the lack of standardization of sensitivity testing, future trials of any antibiotics in any dosage should, for purposes of comparison, be accompanied by data on the range of sensitivity to penicillin and other antibiotics of the strains under study.

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REFERENCES

- Kunin, C. M. (1962). *Proc. exp. Biol. Med.*, **110**, 311.
 Marmell, M., Sills, J. R., and Prigot, A. (1963). "Antimicrobial Agents and Chemotherapy, 1962", p. 502.
 M.R.C. Working Party (1961). *Lancet*, **2**, 226.
 Te-wen Chang and Weinstein, L. (1962). *Antibiot. and Chemother.*, **12**, 676.

Usage de la méthacycline (Rondomycine) dans le traitement de la blennorragie

RÉSUMÉ

La nécessité de tester les antibiotiques récemment découverts pour le traitement de la blennorragie est indiquée à cause de l'efficacité de la pénicilline qui va en diminuant, même si cette efficacité est marginale. Un essai à deux dosages de méthacycline est rapporté.

Les taux de réponses dans les deux dosages ont été presque identiques, de 87,7 pour cent en moyenne.

La suggestion est faite, malgré qu'il n'y ait pas de standardisation pour la sensibilité des tests, que les futurs essais de n'importe quel antibiotique à n'importe quel dosage, devraient être, afin d'être comparés, accompagnés de renseignements sur l'étendue de la sensibilité à la pénicilline des souches étudiées.

ADDENDUM

An independent series of 49 strains of gonococci was tested for the MIC of methacycline. The results were as follows:

MIC (μg./ml.)	Strains
0·06	2
0·25	6
0·5	10
1	12
2	8
4	6
8	5

A single dose of 150 mg. methacycline gives serum levels between 0·39 and 3·12 μg./ml. Higher levels of plasma binding probably exist.

Although the methacycline sensitivity levels of the 49 strains showed a Gaussian distribution similar to the penicillin sensitivity levels of the strains, there was no consistent correlation between methacycline sensitivity and penicillin sensitivity of individual strains.